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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 04/18/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.

09/127,738

Applicant(s)

PONCE DE LEON ET AL.

Examiner

Michael C. Wilson

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 March 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
- ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on 17 March 2003. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☒ The proposed amendment(s) will not be entered because:
- (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet.

3. ☒ Applicant's reply has overcome the following rejection(s): see attached.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☐ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

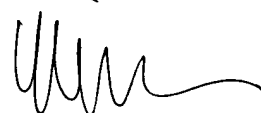
Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: 1-23 25-30.

Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☐ Other: _____



Continuation of 2. NOTE: The proposed limitation of "transferring said cells produced by step (ii) comprising EG cells" (e.g. claim 14) would require an indefiniteness rejection not previously required. Step (ii) requires producing EG cells, not cells comprising EG cells as proposed. .

Continuation of 5. does NOT place the application in condition for allowance because: The arguments have been considered but are not persuasive. See attached. The pending claims remain rejected for reasons of record.

The previous office action included rejections that should have been withdrawn. For clarification, the status of the rejections is set forth herein. Applicants' new arguments are also addressed herein. The proposed amendment filed 3-17-03 has not been entered because it raises new issues. No new rejections are set forth in this advisory action.

Claims 1-23 and 25-30 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a method of obtaining avian EG cells comprising: i) isolating PGCs from an avian embryo; and ii) culturing said PGCs in a culture medium comprising LIF, bFGF and IGF, such that avian EG cells are obtained; 2) a method of making chimeric avians comprising: i) isolating PGCs from an avian embryo; ii) culturing said PGCs in a culture medium comprising: LIF, bFGF and IGF, such that avian EG cells are obtained; iii) transferring said EG cells into a recipient avian embryo; and iv) obtaining a germline and somatic cell chimeric avian, does not reasonably provide enablement for 1) identifying avian EG cells in a mixed population of avian EG cells and PGCs, 2) stably transfecting avian EG cells, or 3) a method of making germline and somatic cell chimeric avians expressing exogenous proteins or having a non-wild-type phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

While the specification enables obtaining EG cells as determined by obtaining germline and somatic cell chimeric chickens (page 37, line 13), the specification does

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not enable identifying avian EG cells within or separating EG cells from a mixed population of avian PGCs and EG cells as encompassed by claims 1, 14, 26, 27 and 30. Pain of record taught obtaining EG cells from Stage X embryos within a mixed population of PGCs and EG cells that provide germline and somatic cell transmission. Pain taught marker proteins found on the mixed population of cells but did not teach the pattern that distinguishes EG cells from PGCs (page 2345, col. 2). Similarly, the specification defines EG cells as being able to produce germline and somatic cell chimeras (page 22, lines 15-21) and teaches administering a mixed population of PGCs and EG cells to a recipient embryo (page 33, line 5). While the specification discusses the staining pattern of EG cells relating to SSEA-1 and 3 marker proteins, and reactivity with EMA-1 and MC-480 antibodies (page 21, line 16 through page 22, line 9), the specification does not provide adequate correlation between staining of SSEA-1 and 3 proteins, or reactivity with EMA-1 and MC-480 antibodies and the ability to produce germline and somatic cell chimeras such that EG cells could be distinguished from PGCs. EMA-1 is not specific to EG cells because it also stains PGCs (page 22, line 1).

Applicants argue that MC-480 reacts strongly with mouse EG cells and avian EG cells cultured after 98 days and weakly with PGCs. Applicants' argument is not persuasive because both avian EG cells and PGCs react with MC-480 (page 42, lines 4-7). The specification does not teach how "strongly" MC-480 must react for a cell to be an avian EG cell.

Claim 10 remains rejected because merely transferring the mixed population of cells to a suitable avian embryo is not adequate to determine whether EG cells have

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been obtained. Transferring the mixed population of cells into an embryo and obtaining somatic cell chimeras that are not germline cell chimeras does not have an enabled use in the instant invention.

Applicants argue somatic chimeras have a well-known use in the art for studying avian development and the interactions of genetically different cell types within an individual and cite Wantanabe. Applicants' argument cannot be considered as the Wantanabe reference has not been provided and is not of record. However, applicants' argument is not persuasive because studying avian development is a generic use and is not specific to somatic chimeras. It cannot be envisioned why one of skill would monitor the interaction of genetically different cell types within a chimera. Applicants argue somatic cell chimeras can be used as food. Applicants' argument is not persuasive because using the avian for food is not specific to the chimeric avian.

Claims 12, 13, 17-19 and 21-23 remain rejected because the specification does not enable transfecting or transforming EG cells with a nucleic acid for reasons of record. The only disclosed purpose for transfecting avian EG cells is to make transgenic avians expressing exogenous proteins or having an altered phenotype (page 7, line 17; page 2, line 23).

Applicants argue that despite the unpredictability in the art for one of skill to express a transgene or to stably transfect EG cells, it would not have required undue experimentation for one of skill to make or use the claimed invention (pg 11, line 1 of response). Applicants argue the avians of Vick could be used for studying reproductive biology because transfected cells can be distinguished from non-transfected cells (pg

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11, 4 lines from the bottom). Applicants' arguments are not persuasive. It cannot be envisioned how distinguishing transfected and non-transfected cells in the gonad reveals anything about reproductive biology. The purpose of Vick is to make a germline chimera that passes on the transgene to its offspring. Failure to obtain such an avian is a clear indication that undue experimentation would be required for one of skill to obtain a germline chimera. Merely transplanting transfected cells into an embryo without expressing the transgene or without passing the transgene on to offspring does not have an enabled use in Vick or elsewhere in the art at the time of filing.

Applicants argue Vick in view of Bosselman and Lee enable one of skill to transfect EG cells and obtain germline chimeric avians as claimed. Applicants argument is not persuasive because Vick, Bosselman and Lee do not teach how to obtain stably transfected EG cells or how to use transfected EG cells to obtain a germline chimeric avian. The examiner does not disagree that it may be possible one day to use transfected EG to make a germline chimeric avian; however, the art at the time of filing taken with the guidance provided in the specification would still leave the person of skill in the art with undue experimentation to determine the parameters required to do so.

Specifically, the specification does not enable transfecting EG cells with DNA encoding a growth factor or enzyme (claims 21 and 23) or isolating an exogenous protein from the egg, systemic circulating system, body fluid or tissue of a chimeric avian (claims 19 and 22). The state of the art at the time of filing was such that the phenotype of transgenic avians with an exogenous transgene was unpredictable (Wall

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of record, 1996, Theriogenology, Vol. 45, pages 57-68; para. bridging pages 61-62).

The specification does not provide adequate guidance for one of skill to reasonably predict that the DNA encoding exogenous proteins would be functionally expressed in transgenic avians, where exogenous protein would be expressed in transgenic avians or that the exogenous protein would have a therapeutic effect. Given the unpredictability in the art taken the teachings provided, the specification does not enable transfecting EG cells with DNA encoding a therapeutic protein or determining whether exogenous protein would be expressed in the egg, systemic circulating system, body fluid or tissue of a chimeric avian.

The rejection of claims 25 and 26 regarding "improving" is withdrawn because the limitation was deleted.

Claims 25 and 28-30, step (ii) must result in obtaining a population of cells comprising EG cells.

Claims 1-23 and 25-30 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The metes and bounds of what applicants consider PGCs cannot be determined. Applicants previously argued the specification distinguishes avian PGCs from avian EG cells in that avian EG cells stain positive for MC-480 (as well as SSEA-1, SSEA-3 and EMA-1 also found of PGCs) and provide germline and somatic cell transmission upon implantation into recipient embryos while avian PGCs do not stain positive for MC-480

and do not provide somatic cell transmission (page 21, line 13 through page 22, line 21). Applicants' argument was not persuasive because PGCs stain positive for MC-480 (page 42, lines 4-7). It cannot be determined what amount of positive staining distinguishes PGCs and EG cells. Therefore, the metes and bounds of cells that are EG cells within a population of PGCs cultured for a period of time in the presence of LIF, bFGF, SCF and IGF are avian EG cells cannot be determined.

Applicants address this rejection on pg 19 of the response but do not discuss the metes and bounds of PGCs. Applicants state identification of specific EG cells or PGCs would not be required. Applicants' argument is not persuasive because claim 1, step (i), for example, requires isolating PGCs. It is unclear if the step is limited to isolating PGCs that become EG cells or if the claim encompasses isolating a population of cells comprising PGCs and EG cells

The rejection of claim 3 because the phrase "said minimum amounts" lacks antecedent basis is withdrawn because claim 3 says "minimal" amounts (see amendment filed 6-3-02, paper number 21).

The rejection of claims 25 and 26 because the preamble is not commensurate in scope with the body of the claim is withdrawn because the claims were amended (see amendment filed 6-3-02, paper number 21).

Claims 25 and 26 remain indefinite because it is unclear if "such PGCs" in (ii) are the PGCs of (i) or some other PGCs that have a similar structure or function.

Claim 25 remains indefinite because it is unclear if "said PGCs" in (iii) are the PGCs of (i) or (ii).

The rejection of claim 25 because the claim does not result in obtaining germline chimeric avians as in the preamble of the claim is withdrawn because the claim has been amended (see amendment filed 6-3-02, paper number 21).

The rejection of claim 25, because "the desired phenotype" lacks antecedent basis and because the term "desired" has variable meanings in the art and is not defined in the specification, has been withdrawn because the phrase has been deleted (see amendment filed 6-3-02, paper number 21).

The rejection of claims 26 and 30, because "said cultured population of primordial germ cells" (iii) lacks antecedent basis in the claims, has been withdrawn because the phrase has been deleted (see amendment filed 6-3-02, paper number 21).

The rejection of claims 26 and 30, because "said isolated, purified PGCs" (iv) lacks antecedent basis in the claims, has been withdrawn because the phrase was deleted (see amendment filed 6-3-02, paper number 21).

The rejection of claims 26 and 30, because "said recipient embryo" (v) lacks antecedent basis in the claims, has been withdrawn because the phrase was deleted (see amendment filed 6-3-02, paper number 21).

The rejection of claims 26, 28 and 30, because avians do not express a phenotype, has been withdrawn because the phrase was deleted (see amendment filed 6-3-02, paper number 21).

The rejection of claim 27, because "the EG cells" lacks antecedent basis, has been withdrawn because the phrase has been deleted (see amendment filed 6-3-02, paper number 21).

The rejection of claims 28 and 29, because "said purified PGCs" (iii) lacks antecedent basis in the claims, has been withdrawn because the term "purified" was deleted (see amendment filed 6-3-02, paper number 21).

Claim Rejections - 35 USC § 102

The rejection of claims 21 and 22 under 35 U.S.C. 102(b) as being anticipated by Chang (1995, Cell Biol. International, Vol. 19, pages 143-149) has been withdrawn because the claims are not directed toward an avian EG cell line as originally filed (see amendment filed June 3, 2002, paper number 21, which amended the claims to method claims).

1. Claims 1, 4-11, 14-16 and 20 remain rejected under 35 U.S.C. 102(b) as being anticipated by Pain (7-25-96, Development, Vol. 122, pages 2239-2348, UnCover online at <http://uncweb.carl.org/uncover/unhome.html>) as evidenced by Simkiss (Simkiss, 1994, MacLean, ed., Animals with novel genes, Transgenic birds, Cambridge Univ. Press, Cambridge England, NY, NY, pages 106-137) and under 35 U.S.C. 102(a) as being anticipated by Pain (Aug. 1996, Development, Vol. 122, pages 2239-2348) as evidenced by Simkiss (Simkiss, 1994, MacLean, ed., Animals with novel genes, Transgenic birds, Cambridge Univ. Press, Cambridge England, NY, NY, pages 106-137) for reasons of record.

The rejection of claim 3 has been withdrawn because it is dependent upon claim 2, which is not included in this rejection. The rejection of claims 21 and 22 has been

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withdrawn because they are no longer directed toward avian EG cells as originally filed (see amendment filed 6-3-02, paper number 21).

Pain taught isolating cells from the blastoderm of a stage X chicken embryo, culturing the cells for more than 160 days in the presence of bFGF, IGF, SCF, LIF without feeder cells (page 2340, col. 1, line 9; page 2340, col. 1, 4th and 5th full paragraphs; page 2345, col. 2, line 10; 2341, col. 2, paragraph 4). The cells expressed EMA-1, SSEA-1 and SSEA-3 for 160 days (page 243, col. 2, last 2 sentences). Simkiss confirms the cells of Pain included PGCs by teaching stage X chicken embryos contain PGCs (page 111, Fig. 4.1, top panel). Pain taught introducing the population of cells into stage X chicken embryos and obtaining germline and somatic cell chimeras (page 2341, col. 1, paragraph 2; page 2346, col. 2, line 8).

Applicants argue Pain does not teach culturing PGCs for at least 14 days in the absence of feeder cells. Applicants' argument is not persuasive. Claims 1, 4-7, 9-11, 14-16 and 20 are not limited to culturing PGCs for at least 14 days. Fig. 2B (page 2342) clearly shows that undifferentiated avian cells were maintained for 5 days in the absence of feeder cells (page 2340, col. 1) which is a time sufficient to produce EG cells as in claims 1, 4-7, 9-11, 14-16 and 20. Claims 6-8 are included because Pain taught culturing the cells for more than 160 days in the presence feeder cells (pg 2343, col. 2, 4 lines from the bottom) and that "the cultures" were maintained with or without feeder cells (page 2341, col. 2, para. 4). All of the cultures discussed by Pain, including the cells having the undifferentiated phenotype cultured for 35 passages (pg 2345), can be

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cultured without feeder cells. Therefore, Pain taught culturing PGCs comprising EG cells for 160 days without feeder cells.

Applicants argue Pain taught away from long-term culture in the absence of feeder cells. Applicants' argument is not persuasive. The claims do not require "long term culture." While Pain taught feeder cells were used, Pain did not teach they were preferred. Pain taught cultures could be made with or without feeder cells. By culturing cells for 160 days with feeder cells, Pain did not "teach away" from culturing without feeder cells. Pain does not state a culture without feeder cells cannot be maintained or discourage one of skill to culture without feeder cells.

The rejection of claims 21 and 22 under 35 U.S.C. 102(e) as being anticipated by Petite (US Patent 5,656,479, Aug. 12, 1997) has been withdrawn because the claims are not directed toward an avian EG cell line as originally filed (see amendment filed June 3, 2002, paper number 21, which amended the claims to method claims).

Claim Rejections - 35 USC § 103

Claims 1 and 2 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pain (Aug. 1996, Development, Vol. 122, pages 2239-2348) as evidenced by Simkiss (Simkiss, 1994, MacLean, ed., Animals with novel genes, Transgenic birds, Cambridge Univ. Press, Cambridge England, NY, NY, pages 106-137) for reasons of record.

Applicants argue Pain did not teach culturing the cells for at least 14 days in the absence of feeder cells. Applicants' argument is not persuasive because the claims do not require culturing cells for 14 days.

Double Patenting

The rejection of claims 1-5, 14-16 and 20-22 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,156,569, Dec. 5, 2000 has been withdrawn in view of the terminal disclaimer.

The rejection of claims 1 and 6-8 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,156,569, Dec. 5, 2000 in view of Pain (1996, Development, Vol. 122, pages 2239-2348) has been withdrawn in view of the terminal disclaimer.

The rejection of claims 1-5, 21 and 22 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 5, 7, 8 and

29-40 of copending Application No. 09/127,624 has been withdrawn in view of the terminal disclaimer.

The rejection of claims 1 and 6-8 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 5, 7, 8 and 29-40 of U.S. Patent No. 09/127624 in view of Pain for reasons of record has been withdrawn in view of the terminal disclaimer.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



**MICHAEL WILSON
PRIMARY EXAMINER**